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Flavonol and flavone intake and the risk of cancer in male smokers (Finland)

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Abstract

Objective: To study the associations between the intake of flavonols and flavones and the risk of cancer.
Methods: The study cohort consisted of 27,110 male smokers, aged 50–69 years, without history of cancer. They were participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in Finland. The men completed a validated dietary questionnaire at baseline. Incident cases of cancers were identified through national registers. During an average 6.1-year follow-up, 791 lung cancers, 226 prostate cancers, 156 urothelial cancers, 133 colorectal cancers, 111 stomach cancers, and 92 renal cell cancers were diagnosed.
Results: Intake of flavonols and flavones was inversely associated with the risk of lung cancer; multivariate relative risk in the highest *vs*. the lowest quartile 0.56, 95% confidence interval 0.45–0.69, p for trend 0.0001. The risk was similar in all histological types of lung cancer. No association was found between flavonol and flavone intake and the risk of other cancers.
Conclusions: Intake of flavonols and flavones seemed to be inversely associated with the risk of lung cancer, but not with that of other cancers.

Introduction

Flavonols and flavones, especially quercetin, have proven to be anticarcinogenic substances [1–6]. Quercetin seems to be a strong *in-vitro* antiproliferative agent against colorectal, ovarian, lymphoid, and breast cancer cells [1, 2]. Quercetin has also been shown to inhibit carcinogen-induced mammary, colonic, oral, and lung neoplasia in rodents [7–10] and DNA adducts in human hepatoma cells [11]. The anticarcinogenic property of flavonols and flavones is most frequently attributed to their antioxidant activity. They can act as antioxidants in several ways: chelating metals and serving as reducing agents, scavenging reactive oxygen species, breaking oxidative chain reactions, quenching the formation of singlet oxygen, and protecting vitamin C from oxidation [12]. Flavonols and flavones can also affect various metabolic pathways; *e.g*. activation of proteolytic enzymes [13]. Furthermore, quercetin is shown to induce chromatin condensation and apoptosis in some cancer cells [2, 14, 15]. Some flavonols and flavones are also potent inhibitors of enzymes involved in signal transduction in cells, *e.g*. protein kinase C, tyrosine kinases, and lipid kinases [13].

On the other hand, flavonoids can also act as pro-oxidants [16, 17]. In addition, quercetin has in one study stimulated oral squamous carcinoma cell growth and DNA synthesis [18], and in another potentiated the mutagenic effect of heterocyclic aromatic amines in murine liver [19].

There are only three cohort studies on the association between the intake of flavonols and flavones and the risk of cancers [20–22], and only one of them found an inverse association [22]. The results have also been contradictory in case–control studies [23–28]. Therefore more studies, especially cohort studies, are necessary to understand the role of flavonols and flavones in the development of cancer. We investigated the association between the intake of flavonols and flavones and the risk of several cancers in a cohort of male smokers.

Materials and methods

Alpha-tocopherol, beta-carotene cancer prevention study

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a double-blind, placebo-controlled, primary prevention trial undertaken to determine whether supplementation with α-tocopherol, β-carotene, or both would reduce the incidence of lung cancer in male smokers. The rationale, design, and methods of the study, as well as the characteristics of the participants, have been described in detail elsewhere [29].

Participants of the ATBC study were recruited in 1985–1988 from the total male population aged 50–69 years in southwestern Finland (n = 290,406). To be eligible the subjects had to be smokers of at least five cigarettes per day at entry and give written informed consent. Exclusion criteria included a history of cancer or other serious disease limiting long-term participation; use of vitamin E, vitamin A, or β-carotene supplements in excess of predefined doses; and treatment with anticoagulant agents.

Eligible men (n = 29,133) were randomized into one of four supplementation regimens: α-tocopherol alone (daily dose 50 mg), β-carotene alone (20 mg), α-tocopherol and β-carotene, or placebo. Trial follow-up continued for 5–8 years (median 6.1 years).

Baseline measurements

At baseline the men completed a questionnaire on general background characteristics, and medical and smoking histories. Height and weight were measured, and serum samples were collected and stored at −70 °C. A chest X-ray was taken to exclude existing lung cancer.

Dietary assessment

Diet was assessed at baseline using a self-administered, modified diet history method [30]. The diet questionnaire included 276 food items and mixed dishes. It was used with a portion-size picture booklet of 122 photographs of foods, each with three to five different portion sizes. The subject was asked to report the frequency of consumption and the usual portion size of foods during the previous 12 months. Frequencies were reported as the number of times per month, week, or day. At the first baseline visit the questionnaire, along with the picture booklet, was given to the subject to be completed at home. At the second baseline visit, 2 weeks later, the questionnaire was returned, reviewed, and completed together with a study nurse. The questionnaire was satisfactorily completed by 27,110 participants (93%).

Food-consumption data were computed into daily nutrient intake values based on the food composition database and related software at the National Public Health Institute, Finland. Flavonol and flavone content of foods are based mainly on composition analyses done by Hertog and colleagues [31, 32]. The flavonol content of berries is, however, based on Finnish analyses [33]. Onions were included in intake calculation through recipes. White and red wine were not asked separately in the questionnaire; thus it was supposed that half of the wine was white and the other half red. This estimate was derived from Finnish alcohol consumption statistics. Total flavonol and flavone intake was calculated as the sum of intakes of quercetin, kaempherol, myricetin, luteolin, and apigenin. Of these quercetin, kaempherol, and myricetin are flavonols and luteolin and apigenin are flavones. Quercetin comprised 85.1%, kaempherol 5.7%, myricetin 8.4%, luteolin 0.3%, and apigenin 0.5% of the total intake of flavonols and flavones.

The dietary method was validated in a pilot study carried out among 190 men prior to the ATBC study [30]. The men completed the questionnaire first and then kept food records for 24 days, spread over 6 months, as the reference method. They filled in the questionnaire again at the end of the study. The energy-adjusted Pearson correlations between the first and second questionnaires and food records were 0.59 and 0.66, respectively, for flavonols and flavones.

Ascertainment of endpoints

This study included all incident cases of lung cancer (n = 791), bladder cancer and cancers of the ureter and renal pelvis (urothelial cancers, n = 156), renal cell cancer (n = 92), prostate cancer (n = 226), colorectal cancer (n = 133), and stomach cancer (n = 111) diagnosed between May 1985 and April 1993, and identified through the Finnish Cancer Registry and the Register of Causes of Death. The medical records of each case were centrally reviewed by study physicians, including oncologists, to confirm diagnoses. Histopathologic and cytologic specimens were also obtained for central review.

Statistical analysis

Participants contributed follow-up time from the date of randomization until first cancer, death, or end of trial (30 April 1993). Intake of flavonols and flavones, and nutrients were log-transformed and then energy-adjusted by the regression residual method [34]. Alcohol intake was not energy-adjusted. Men were grouped into quartiles of energy-adjusted intakes of flavonols and flavones, and

nutrients. Proportional hazards models were used to estimate relative risks (95% confidence intervals) of cancers associated with different intake levels of flavonols and flavones. The relative risks were adjusted for age, supplementation group, and in smoking-related cancers, also for years of smoking and number of cigarettes daily (lung, renal cell, and urothelial cancers). The risks were further adjusted for other potential risk factors: education, and dietary intakes of β-carotene, folic acid, and vitamins C and E. Tests for linearity of the trend were obtained from the Wald test by treating median values of each quartile as continuous variables in the proportional hazards model. The main analyses were repeated for lung cancer in the placebo group of the trial cohort, whereas the numbers of other cancers were too small for meaningful analyses in the placebo group alone.

Results

Baseline characteristics of cancer cases and non-cases are presented in Table 1. Cancer cases of all cancers were older than the non-cases. Lung cancer cases were less educated, and prostate cancer cases more educated than non-cases. In addition, there were fewer tea or wine drinkers among lung cancer cases than among non-cases. Median intake of flavonols and flavones was lower in cases of lung and renal cell cancer than in non-cases, whereas for other cancers, no difference was found. Lung cancer cases had lower consumption of vegetables, fruits, and berries than non-cases.

Intake of flavonols and flavones was inversely associated with the risk of lung cancer (Table 2). The relative risk (RR) was 0.56 (95% confidence interval (CI) 0.45–0.69, p for trend 0.0001) in the highest *vs*. the lowest quartile, adjusted for age, supplementation group, number of cigarettes smoked daily, and years of smoking. After further adjustment for education, and intakes of folic acid, vitamin C, and beta-carotene, the relative risk was changed only slightly (RR 0.61, 95% CI 0.48–0.77, p for trend 0.0001). The association in the placebo group was similar to that of the whole cohort (multivariate RR 0.50, 95% CI 0.31–0.80, p for trend 0.0009). Relative risks for different histological types of lung cancer were similar (Table 3). Of the individual flavonols and flavones, quercetin (RR 0.63, 95% CI 0.52–0.78, p for trend 0.0001), myricetin (RR 0.68, 95% CI 0.55–0.84, p for trend 0.0001), and kaempherol (RR 0.61, 95% CI 0.50–0.75, p for trend 0.0001) were

Table 1. Baseline characteristics of study participants by cancer[a]

Characteristics	No cancer	Lung cancer	Urothelial cancer	Renal cell cancer	Prostate cancer	Colorectal cancer	Stomach cancer
No.	25,643	791	156	92	226	133	111
Median of							
Age (years)	56.9	60.4	60.4	59.1	61.9	59.4	58.9
Smoking (years)	37	40	38	38	37	37	37
No of cigarettes per day	19	20	20	20	17	18	19
Body mass index (kg/m^2)	26.0	25.2	25.6	26.6	26.2	26.1	25.8
Percentage of group							
Education (>11 years)	10.5	6.1	9.1	11.6	18.0	7.8	10.1
Wine drinkers ($\geq$1 glass) per week	11.5	8.8	7.7	10.7	10.2	13.9	9.5
Tea drinkers ($\geq$1 cup) per day	16.9	11.6	13.7	15.6	16.9	22.9	23.8
Median daily intake of							
Flavanols and flavones (mg)	8.1	6.9	8.0	7.0	8.3	8.5	8.9
Energy (kcal)	2730	2640	2680	2730	2700	2830	2600
Fiber (g)	24.3	22.4	23.9	23.9	23.5	24.8	23.6
Alcohol (g)	11.3	11.8	7.0	9.7	11.8	12.5	11.0
Vitamin C (mg)	88.3	81.3	96.9	88.4	86.6	93.7	88.2
Vitamin E (mg)	10.8	9.9	10.8	10.6	10.6	11.9	10.2
Folic acid (g)	326	309	336	325	310	326	320
β-carotene (μg)	1710	1610	2040	1780	1750	1740	1590
Median daily consumption of							
Vegetables (g)	94.5	84.0	114.1	100.2	88.6	101.7	92.6
Fruits (g)	70.7	59.2	79.7	72.0	74.9	83.0	85.5
Berries (g)	26.4	22.5	22.3	22.3	31.0	25.7	31.5

[a] Directly age-standardized to distribution of entire cohort.

Table 2. Intake of flavonols and flavones, and relative risks (RR, 95% confidence intervals) of smoking-related cancers

	Quartile of intake				*p* for trend
	1	2	3	4	
Median intake (mg/day)	4.2	6.7	9.6	16.3	
Lung cancer					
Number of cases	257	226	185	123	
Age-adjusted RR[a]	1.0	0.91 (0.76–1.1)	0.74 (0.62–0.90)	0.50 (0.40–0.62)	0.0001
Multivariate RR[b]	1.0	0.95 (0.80–1.1)	0.81 (0.67–0.98)	0.56 (0.45–0.69)	0.0001
Urothelial cancer					
Number of cases	32	47	39	38	
Age-adjusted RR[a]	1.0	1.4 (0.90–2.2)	1.2 (0.73–1.8)	1.1 (0.71–1.8)	0.88
Multivariate RR[b]	1.0	1.4 (0.91–2.2)	1.2 (0.75–1.9)	1.2 (0.73–1.8)	0.77
Renal cell cancer					
Number of cases	33	20	19	20	
Age-adjusted RR[a]	1.0	0.60 (0.35–1.1)	0.61 (0.35–1.1)	0.61 (0.35–1.1)	0.07
Multivariate RR[b]	1.0	0.61 (0.35–1.1)	0.63 (0.36–1.1)	0.63 (0.36–1.1)	0.10

[a] Adjusted for age and supplementation group.
[b] Adjusted for age, supplementation group, years of smoking, and number of cigarettes per day.

Table 3. Intake of flavonols and flavones, and relative risk[a] (95% confidence intervals) of lung cancer by histological type

	Quartile of intake				*p* for trend
	1	2	3	4	
Median intake (mg/day)	4.2	6.7	9.6	16.3	
Squamous cell (n = 344)	1.0	0.98 (0.76–1.3)	0.78 (0.58–1.0)	0.43 (0.30–0.61)	0.0001
Small cell (n = 173)	1.0	1.1 (0.72–1.5)	0.76 (0.50–1.2)	0.63 (0.41–0.99)	0.02
Adenocarcinoma (n = 131)	1.0	0.65 (0.41–1.0)	0.88 (0.57–1.4)	0.51 (0.30–0.85)	0.03
Other or unknown (n = 143)	1.0	1.1 (0.73–1.7)	0.88 (0.55–1.4)	0.85 (0.54–1.4)	0.35

[a] Adjusted for age, supplementation group, years of smoking, and number of cigarettes per day.

significantly inversely associated with the risk of lung cancer, whereas no associations were observed for luteolin and apigenin.

The risk of renal cell cancer was 40% lower, albeit not significantly, from the second to the fourth quartile of flavonol and flavone intake as compared with the lowest intake (Table 2). No association was found between the risk of urothelial cancer and the intake of flavonols and flavones.

Cancers of the prostate or stomach were not associated with the intake of flavonols and flavones (Table 4). The risk of colorectal cancer was significantly higher in the highest quartile of intake than in the lowest, but the association was not linear.

In food group analysis, the consumption of vegetables, fruits, and berries was inversely associated with the risk of lung cancer (Table 5). In addition, the risk of lung cancer was lower among those who drank on average at least one cup of tea per day or one glass of wine per week as compared with those drinking less. When flavonol and flavone intake was added to food group models the association between the risk of lung cancer and the consumption of vegetables was attenuated to some extent (RR 0.79, 95% CI 0.63–0.99, *p* for trend 0.04), whereas for other food the associations became non-significant. In all these models the intake of flavonols and flavones retained its significance. In a multivariate model which simultaneously included all foods (vegetables, fruits, berries, tea, wine), the relative risks of lung cancer were similar to those when foods were included one at a time to the model, except for fruits and berries, for which the association became non-significant.

Discussion

We observed an inverse association between the intake of flavonols and flavones and the risk of lung cancer in male smokers. The association was similar for all main histological types of lung cancer. Inverse associations between the main flavonol and flavone sources, vegeta-

Table 4. Intake of flavonoles and flavones, and relative risks[a] (RR, 95% confidence intervals) of cancers not related to smoking

	Quartile of intake				*p* for trend
	1	2	3	4	
Median intake (mg/day)	4.2	6.7	9.6	16.3	
Prostate cancer					
Number of cases	51	57	57	61	
RR	1.0	1.1 (0.78–1.6)	1.2 (0.80–1.7)	1.3 (0.87–1.8)	0.24
Colorectal cancer					
Number of cases	26	38	27	42	
RR	1.0	1.5 (0.89–2.4)	1.1 (0.62–1.8)	1.7 (1.0–2.7)	0.10
Stomach cancer					
Number of cases	29	25	24	33	
RR	1.0	0.87 (0.51–1.5)	0.92 (0.54–1.6)	1.2 (0.71–1.9)	0.51

[a] Adjusted for age and supplementation group.

Table 5. Consumption of foods rich in flavonols and flavones, and relative risk[a] (RR, 95% confidence intervals) of lung cancer

	Number of cases	RR (95% CI)
Vegetables[b]		
<59 g/day	246	1.0
59–94 g/day	218	0.99 (0.82–1.2)
95–142 g/day	192	0.88 (0.73–1.1)
>142 g/day	135	0.67 (0.55–0.83)
p for trend		0.0002
Fruits[b]		
<32 g/day	239	1.0
32–70 g/day	204	0.91 (0.76–1.1)
71–120 g/day	197	0.91 (0.75–1.1)
>120 g/day	151	0.73 (0.60–0.90)
p for trend		0.005
Berries[b]		
<12 g/day	222	1.0
12–26 g/day	211	0.98 (0.81–1.2)
27–49 g/day	183	0.88 (0.72–1.1)
>49 g/day	175	0.83 (0.68–1.0)
p for trend		0.03
Tea		
Less than one cup (170 ml)/day	696	1.0
At least one cup/day	95	0.66 (0.54–0.82)
Wine		
Less than one glass (120 ml)/week	730	1.0
At least one glass/week	61	0.70 (0.54–0.91)

[a] Adjusted for age, supplementation group, years of smoking, and number of cigarettes per day.
[b] Classification based on quartiles.

bles, fruits, berries, tea, and wine, and lung cancer risk were also observed. Intake of flavonols and flavones had no consistent association with the risk of other cancers.

Our study has many strengths. Its prospective nature eliminated bias in dietary recall due to disease. The sizeable cohort with a long follow-up provided the large number of cancer cases necessary to detect small differences in cancer risk. The cases were identified through the Finnish Cancer Register, which has almost 100% case ascertainment [35]. Since lung cancer was the primary endpoint in the ATBC study, special efforts were undertaken to promote its detection. At baseline a chest X-ray was taken to exclude existing lung cancers and the chest X-ray was repeated every 28 months, and at the end of the study, to enhance detection of lung cancer.

The biggest weakness of our study was with the validity and accuracy of flavonol and flavone intake. Since the food-frequency questionnaire was not designed to estimate the intake of flavonols and flavones, two foods are problematic: wine and onions. Red and white wines, which differ greatly in their flavonol and flavone content, were not asked about separately in the food-frequency questionnaire. This, however, does not cause a very large bias, since on average only 1.9% of flavonols and flavones are derived from alcoholic beverages. The second problem is onions. Onion intake is mostly as a spice in recipes, which is assumed to be the same for everybody. Nevertheless, a large variation could exist in the use of onions in cooking; some persons abstain from using onions for either medical reasons (*e.g.* gallstones, dyspepsia, flatulence, irritable bowel disease) or other reasons (*e.g.* aversion). In these cases, the intake of quercetin is overestimated. This problem exists not only in our study, however, but in most studies that use food-consumption data.

Results of the association between the flavonol and flavone intake and the risk of cancer in epidemiologic studies have been inconsistent. In an ecological study comparing 16 cohorts in seven countries the intake of flavonols and flavones was not associated with cancer mortality [36]. In case–control studies inverse

associations have been observed between the flavonol and flavone intake and the risk of gastric cancer [25], upper aerodigestive tract cancer [26], and lung cancer [27], and between the quercetin intake and lung cancer, especially squamous cell carcinoma [28]. However, in other case–control studies no association was seen between the intake of any flavonols or flavones and the risk of lung cancer [23] or bladder cancer [24].

Three published prospective studies have investigated the association between flavonol and flavone intake and the risk of cancer. In a Dutch cohort study of 738 men, no association was observed between intake and the incidence of cancer or mortality from all causes [20]. In a cohort of 9959 Finns, an inverse relationship was found between the intake and the risk of lung cancer, RR 0.54 (95% CI 0.34–0.87) [22]. In a study carried out in South Wales, consisting of 2512 men, flavonol and flavone intake was unrelated to the risk of cancer death [21]. Thus, some evidence exists from previous studies in support of an inverse association between flavonol and flavone intake and lung cancer, in line with the present findings. Experimental research also gives some support to the possible beneficial effect of flavonols and flavones in lung cancer; quercetin has in many studies inhibited the carcinogenic action of polycyclic aromatic hydrocarbons [7, 11, 37–42], which form the major group of carcinogens in tobacco smoke.

The association between tea consumption and the risk of lung cancer has been investigated in several studies. Of the three case–control studies, the first showed an inverse association between tea drinking and the risk of lung cancer [43]. The second indicated that regular tea drinking was directly associated with risk, while decaffeinated tea drinking was inversely associated with risk [44]. In the third study, no relation was found between tea drinking and risk [28]. Of the four prospective studies, three showed no association with lung cancer risk [44–46], and in one tea drinking was associated directly with all-cause cancer mortality [47]. Thus, previous epidemiologic studies do not support our results showing decreased risk of lung cancer with increased tea consumption.

It could be argued that the inverse association with tea is due not to flavonols and flavones, but to catechins, since the amount of catechins in tea is much higher than that of flavonols and flavones. However, experimental research does not support this idea, since quercetin, and other flavonols and flavones, are found to have stronger anticarcinogenic properties than catechins [1–6]. Furthermore, in our study, intake of flavonols and flavones retained its significance even after adjusting for consumption of tea, whereas tea lost its significance after adjusting for flavonols and flavones. This indicates that intake of flavonols and flavones has an independent association with the risk of lung cancer, while at the same time mediating the inverse association between tea drinking and lung cancer risk.

The lower risk of lung cancer in wine drinkers was probably not due to flavonols and flavones in wine, since wine drinkers obtained on average only 0.2 mg flavonols and flavones from alcoholic beverages. Neither was the total intake of flavonols and flavones a plausible explanation for the lowered risk in wine drinkers, because the difference in flavonol and flavone intake was only 3 mg/day between those drinking on average at least one glass of wine per week and those drinking less [48]. Wine drinkers are a very specific group of people in Finland – they tend to be more highly educated and urban-dwelling than those who do not drink wine. Thus, although several background factors were taken into account in risk estimates, some residual confounding probably remained. The most likely explanation for the lowered risk of lung cancer among wine drinkers is differences in other lifestyle factors.

The evidence for the lowered risk of cancer with high consumption of vegetables, fruits, and berries is quite consistent, particularly for lung cancer [49]. Flavonols and flavones are not, however, the only compounds which might account for these associations. For example, carotenoids, coumarins, isothiocyanates, and allium compounds could lie behind these associations. This is supported by our findings, since the risk of lung cancer was attenuated only slightly after adjustment for intake of flavonols and flavones.

In conclusion, high intake of flavonols and flavones was related to a lowered risk of lung cancer, but not to other cancers in male smokers. In addition, consumption of foods rich in flavonols and flavones, especially tea and vegetables, was inversely associated with the risk of lung cancer. Additional large-scale prospective studies are needed, however, to determine the role of flavonols and flavones in the etiology of cancer.

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References

1. Agullo G, Gamet-Payrastre L, Fernandez Y, Anciaux N, Demigné C, Rémésy C (1996) Comparative effects of flavonoids on the growth, viability and metabolism of a colonic adenocarcinoma cell line (HT29 cells). *Cancer Lett* **105**: 61–70.

2. Kuo SM (1996) Antiproliferative potency of structurally distinct dietary flavonoids on human colon cancer cells. *Cancer Lett* **110**: 41–48.
3. Zeng LH, Wu J, Fung B, Tong JH, Mickle D, Wu TW (1997) Comparative protection against oxyradicals by three flavonoids on cultured endothelial cells. *Biochem Cell Biol* **75**: 717–720.
4. Fotsis T, Pepper MS, Aktas E, *et al*. (1997) Flavonoids, dietary-derived inhibitors of cell proliferation and *in vitro* angiogenesis. *Cancer Res* **57**: 2916–2921.
5. Kawaii S, Tomono Y, Katase E, Ogava K, Yano M (1999) Antiproliferative activity of flavonoids on several cancer cell lines. *Biosci Biotechnol Biochem* **63**: 896–899.
6. Kawaii S, Tomono Y, Katase E, Ogawa K, Yano M (1999) Effect of citrus flavonoids on HL-60 cell differentiation. *Anticancer Res* **19**: 1261–1270.
7. Verma AK, Johnson JA, Gould MN, Tanner MA (1988) Inhibition of 7,12-dimethylbenz(*a*)anthracene- and *N*-nitrosomethylurea-induced rat mammary cancer by dietary flavonol quercetin. *Cancer Res* **48**: 5754–5758.
8. Deschener EE, Ruperto J, Wong G, Newmark HL (1991) Quercetin and rutin as inhibitors of azoxymethanol-induced colonic neoplasia. *Carcinogenesis* **12**: 1193–1196.
9. Makita H, Tanaka T, Fujitsuka H, *et al*. (1996) Chemoprevention of 4-nitroquinoline 1-oxide-induced rat oral carcinogenesis by the dietary flavonoids chalcone, 2-hydroxychalcone, and quercetin. *Cancer Res* **56**: 4904–4909.
10. Khanduja KL, Gandhi RK, Pathania V, Syal N (1999) Prevention of *N*-nitrosodiethylamine-induced lung tumorigenesis by ellagic acid and quercetin in mice. *Food Chem Toxicol* **37**: 313–318.
11. Kang ZC, Tsai SJ, Lee H (1999) Quercetin inhibits benzo[*a*]pyrene-induced DNA adducts in human Hep G2 cells by altering cytochrome P-450 1A1 gene expression. *Nutr Cancer* **35**: 175–179.
12. Kandaswami C, Middleton E (1994) Free radical scavenging and antioxidant activity of plant flavonoids. *Adv Exp Med Biol* **366**: 351–376.
13. Gamet-Payrastre L, Manenti S, Gratacap MP, Tulliez J, Chap H, Payrastre B (1999) Flavonoids and the inhibition of PKC and PI-kinase. *Gen Pharmacol* **32**: 279–286.
14. Csokay B, Prajda N, Weber G, Olah E (1997) Molecular mechanisms in the antiproliferative action of quercetin. *Life Sci* **60**: 2157–2163.
15. Wei YQ, Kariya Y, Fukata H, Teshigawara K, Uchida A (1994) Induction of apoptosis by quercetin: involvement of heat shock protein. *Cancer Res* **54**: 4952–4957.
16. Sahu SC, Gray GC (1996) Pro-oxidant activity of flavonoids: effects of glutathione and glutathione *S*-transferase in isolated rat liver nuclei. *Cancer Lett* **104**: 193–196.
17. Galati G, Chan T, Wu B, O'Brien PJ (1999) Glutathione-dependent generation of reactive oxygen species by the peroxidase-catalyzed redox cycling of flavonoids. *Chem Res Toxicol* **12**: 521–525.
18. ElAttar TMA, Virji AS (1993) Modulating effect of resveratrol and quercetin on oral cancer cell growth and proliferation. *Anticancer Drugs* **10**: 187–193.
19. Rowland I (1993) Dietary modification of the activity of food mutagens. *Mutagenesis* **8**: 476.
20. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D (1994) Dietary flavonoids and cancer risk in the Zutphen Elderly Study. *Nutr Cancer* **22**: 175–184.
21. Hertog MGL, Sweetnam PM, Fehily AM, Elwood PC, Kromhout D (1997) Antioxidant flavonols and ischemic heart disease in a Welsh population of men – the Caerphilly Study. *Am J Clin Nutr* **65**: 1489–1494.
22. Knekt P, Järvinen R, Seppänen R, *et al*. (1997) Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *Am J Epidemiol* **146**: 223–230.
23. Garcia-Closas R, Agudo A, Gonzalez CA, Riboli E (1998) Intake of specific carotenoids and flavonoids and the risk of lung cancer in women in Barcelona, Spain. *Nutr Cancer* **32**: 154–158.
24. Garcia R, Gonzalez CA, Agudo A, Riboli E (1999) High intake of specific carotenoids and flavonoids does not reduce the risk of bladder cancer. *Nutr Cancer* **35**: 212–214.
25. Garcia-Closas R, Gonzales CA, Agudo A, Riboli E (1999) Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. *Cancer Causes Control* **10**: 71–75.
26. Stefani ED, Ronco A, Mendilaharsu M, Deneo-Pellegrini H (1999) Diet and risk of cancer of the upper aerodigestive tract – II: Nutrients. *Oral Oncol* **35**: 22–26.
27. Stefani ED, Boffetta P, Deneo-Pellegrini H, *et al*. (1999) Dietary antioxidants and lung cancer risk – a case–control study in Uruguay. *Nutr Cancer* **34**: 100–110.
28. Le Marchand, Murphy SP, Hankin JH, Wilkens LR, Kolonel LN (2000) Intake of flavonoids and lung cancer. *J Natl Cancer Inst* **19**: 154–160.
29. The ATBC Cancer Prevention Study Group (1994) The Alpha-Tocopherol, Beta-Carotene Lung Cancer Study: design, methods, participant characteristics, and compliance. *Ann Epidemiol* **4**: 1–10.
30. Pietinen L, Hartman AM, Haapa E, *et al*. (1998) Reproducibility and validity of dietary assessment instruments. I: A self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol* **128**: 655–666.
31. Hertog MGL, Hollman PC, Katan MB (1992) Content of potentially anticarcinogenic flavonoids of 28 vegetables and 9 fruits commonly consumed in the Netherlands. *J Agric Food Chem* **40**: 2379–2383.
32. Hertog MGL, Hollman PC, van de Putte P (1993) Content of potentially anticarcinogenic flavonoids in tea infusions, wines, and fruit juices. *J Agric Food Chem* **41**: 1242–1246.
33. Häkkinen SH, Kärenlampi SO, Heinonen IM, Mykkänen HM, Törrönen AR (1999) Content of the flavonols quercetin, myricetin and kaempherol in 25 edible berries. *J Agric Food Chem* **47**: 2274–2279.
34. Willett WC, Stampfer MJ (1986) Total energy intake – implications for epidemiologic analyses. *Am J Epidemiol* **124**: 17–27.
35. Teppo L, Pukkala L, Lehtonen M (1994) Data quality and quality control of a population-based cancer registry – experience in Finland. *Acta Oncol* **33**: 365–369.
36. Hertog MGL, Kromhout D, Aravanis C, *et al*. (1995) Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. *Arch Intern Med* **155**: 381–386.
37. Wargovich MJ, Eng VW, Newmark HL (1985) Inhibition of plant phenols by benzo(*a*)pyrene-induced nuclear aberrations in mammalian intestinal cells: a rapid *in vivo* assessment method. *Food Chem Toxicol* **23**: 47–49.
38. Ogawa S, Hirayma T, Nohara M, Tokuda M, Hirai K, Fukui S (1985) The effect of quercetin on the mutagenicity of 2-acetylaminofluorene and benzo[alpha]pyrene in *Salmonella typhimurium* strains. *Mutat Res* **142**: 103–107.
39. Sousa RL, Marletta MA (1985) Inhibition of cytochrome P-450 activity in rat liver microsomes by the naturally occurring flavonoid, quercetin. *Arch Biochem Biophys* **240**: 345–357.
40. Das M, Khan WA, Asokan P, Bickers DR, Mukhtar H (1987) Inhibition of polycyclic aromatic hydrocarbon–DNA adduct formation in epidermis and lung of SENCAR mice by naturally occurring plant phenols. *Cancer Res* **47**: 767–773.

41. Mukhtar H, Das M, Khan WA, Wang ZY, Bik DP, Bickers DR (1988) Exceptional activity of tannic acid among naturally occurring plant phenols in protecting against 7,12-dimethylbenz(*a*)anthracene-, benzo(*a*)pyrene, 3-methylcholanthrene-, and *N*-methyl-*N*-nitrosourea-induced skin tumorigenesis in mice. *Cancer Res* **48**: 2361–2365.
42. Le Bon AM, Siess MH, Suschetet M (1992) Inhibition of microsome-mediated binding of benzo[*a*]pyrene to DNA by flavonoids either *in vitro* or after dietary administration to rats. *Chem Biol Interact* **83**: 65–71.
43. Mendilaharsu M, De Stefani E, Deneo-Pellegrini H, Carzoglio JC, Ronco A (1998) Consumption of tea and coffee and the risk of lung cancer in cigarette-smoking men: a case–control study in Uruguya. *Lung Cancer* **19**: 101–107.
44. Mohr DL, Blot WJ, Tousey PM, Van Doren ML, Wolfe KW (1999) Southern cooking and lung cancer. *Nutr Cancer* **35**: 34–43.
45. Heilbrun LK, Nomura A, Stemmerman GN (1986) Black tea consumption and cancer risk: a prospective study. *Br J Cancer* **54**: 677–683.
46. Goldbohm RA, Hertog MGL, Brants HAM, van Poppel G, van den Brandt PA (1996) Consumption of black tea and cancer risk: a prospective cohort study. *J Natl Cancer Inst* **88**: 93–100.
47. Zheng W, Doyle TJ, Kushi LH, Sellers TA, Hong CP, Folsom AR (1996) Tea consumption and cancer incidence in a prospective cohort study of postmenopausal women. *Am J Epidemiol* **144**: 175–182.
48. Hirvonen T, Pietinen P, Virtanen M, *et al.* (2001) Intake of flavonols and flavones and risk of coronary heart disease in male smokers. *Epidemiology* **12**: 62–67.
49. Steinmetz KA, Potter JD (1996) Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc* **96**: 1027–1039.